GTL Solvents

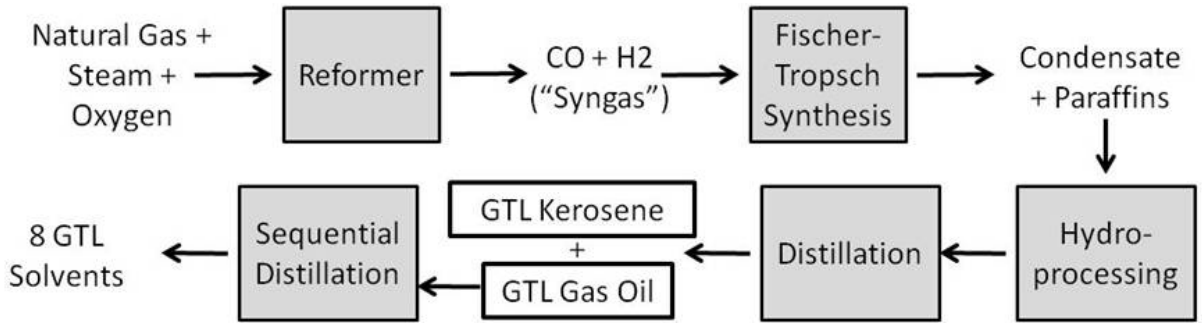
GS1927 and GS2735 notification

Expert human health hazard assessment

1. Introduction and Read Across Strategy.

GTL-Solvents are produced by the sequential fractional distillation of "*Distillates (Fischer-Tropsch), C8 – C26, branched and linear*" (CAS No.: 848301-67-7), also known as *GTL Gas Oil or GTL Diesel*. GTL Gas Oil is a complex UVCB containing normal and iso-paraffins of chain length C8-C26. The synthesis of GTL Gas Oil and its subsequence fractionation into GTL Solvents is shown in Figure 1.

Figure 1 - Process for synthesis of GTL Kerosene, GTL Gas Oil and GTL Fractionates



The *GTL-Solvents* range consists of the following products based on distillation 'cuts' of GTL Gas Oil (Table 1).

Table 1: List of GTL solvents products, their chemical names, CAS numbers and GHS classifications

Product	Chemical name[1]	CAS Number
Shell GTL Solvent GS160	Hydrocarbons, C8-C11, n-alkanes, isoalkanes, <2% aromatics	1437281-13-4
Shell GTL Solvent GS170	Hydrocarbons, C9-C12, n-alkanes, isoalkanes, <2% aromatics	1437281-04-3
Shell GTL Solvent GS190	Hydrocarbons, C10-C13, n-alkanes, isoalkanes, <2% aromatics	185857-36-7

Shell GTL Solvent GS210	Hydrocarbons, C9-C13, n-alkanes, isoalkanes, <2% aromatics	1437280-84-6
Shell GTL Solvent GS215	Hydrocarbons, C12-C15, n-alkanes, isoalkanes, <2% aromatics	1437281-03-2
Shell GTL Solvent GS250	Hydrocarbons, C14-C16, n-alkanes, isoalkanes, <2% aromatics	1174918-46-7
Shell GTL Solvent GS270	Hydrocarbons, C15-C19, n-alkanes, isoalkanes, <2% aromatics	1437281-01-0
Shell GTL Solvent GS310	Hydrocarbons, C18-C24, isoalkanes, <2% aromatics	1437280-85-7
Shell GTL Solvent GS1927	Hydrocarbons, C11-16, branched and linear , <2% aromatics	1809170-78-2
Shell GTL Solvent GS2735	Hydrocarbons, C16-22, branched and linear , <2% aromatics	1802246-63-4

[1] The carbon number range presented for GTL solvents is consistent with the Hydrocarbon Solvents Producers Association (HSPA) naming convention [1] that has been adopted within Europe to identify hydrocarbon solvent type products.

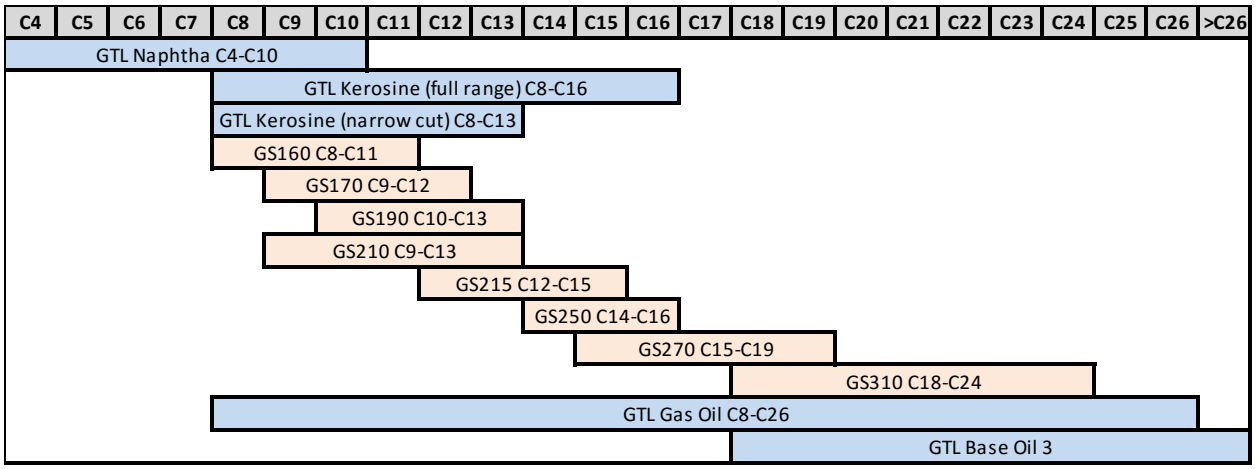
This document is an evaluation of the human hazard properties of *GTL-Solvents* based on available data on the GTL-Solvents themselves or from related GTL substances: GTL Gas Oil, GTL Kerosine and substances with analogue hydrocarbon constituents. Using data from these related GTL substances is reasonable, because of their overlapping hydrocarbon constituent's profile. In other words, data on GTL substances with a broader carbon number range can be used to predict the mammalian toxicity hazards of GTL-Solvents with narrower carbon number ranges based on the so called "read-across" approach.

The "read across "approach is based on the premise that substances which are chemically similar in e.g. their functional groups, chemical structures and physical chemical properties, can be grouped together and jointly assessed for their toxicological properties. Available toxicity data of a representative substance in the group can be used to "read-across" to the rest of the substances of the same group assuming that, based on their analogue chemical profiles, the toxicity will not be significantly different among them. [1]

A strong "read-across" approach requires that the available data covers areas of uncertainty, such as *variability* of the substances, which rely on "read-across" to predict their toxicity. For the GTL-Solvents a clear variation is carbon chain length. Confidence in "reading-across" from existing data of GTL products (e.g. Kerosine, Gas Oil) is justified, because data on these substances cover all the *GTL-Solvents* carbon chain range: from bottom (C8) to the top (C24). Thus read across will be done by interpolation as visualized in the Figure 2.

[1] The use of a category approach to support read-across of data is endorsed by the OECD, and the approach is described in the guidance document, Guidance on Grouping of Chemicals (OECD, 2014) http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en.

Figure 2: Illustration of carbon number ranges of representative GTL Solvents and related products



As can be seen from Figure 1, GTL Solvent's carbon ranges are within the carbon range of the read across substances, either GTL Kerosine or GTL Gas Oil (or both).

As can be seen in more detail in the following section, using read across from analogue substances with acute and repeated dose experimental data does not indicate that *GTL Solvents* in any of its different 'cuts' (as defined by boiling point and carbon chain length) are of concern for toxic effects in human health.

There are however some hazards associated with physical chemical properties, transient effects and skin irritation:

- Because of their low viscosity, all GTL Solvents products should be classified as: *"Aspiration Hazard Cat.1 - H304"* under the Globally Harmonised System of Classification and Labeling of Chemicals (GHS).
- GTL solvents containing carbon numbers $\leq$ C9 may cause drowsiness and dizziness, which merit having an additional hazard classification for human health: "STOT SE Cat.3 –H336".
- GTL solvents with carbon ranges C8-C11 and C9-C12 are irritating to the skin, and thus should be classified and labelled: Skin Irritation Category 2 - H315 *Causes skin irritation.*
- The hazard for skin defatting is recognized for all GTL solvent 'cuts', thus the previous classifications should be typically accompanied with the warning *'Repeated exposure may cause skin dryness or cracking'* appearing in the MSDS under chapter 2 and 11.

2. GTL- Solvents Mammalian Health Hazard Assessment

The health hazard assessment of *GTL-Solvents* is based on data on the actual product or from substances with similar composition of hydrocarbon constituents (normal and iso alkanes), such as GTL diesel, GTL Kerosine and analogue aliphatic substances, which contain similar constituents but at different proportions. Based on their aliphatic character, these products have predictable toxicokinetic properties and have thus produced similar results in acute and repeated dose toxicity studies.

2.1 Toxicokinetics

Oral studies with various complex substances (UVCB) containing normal, branched and cyclic aliphatic constituents show that after a single oral dose, absorption is inversely correlated with carbon chain length and independent of isomeric form, preparation process, or type of product [2].

Dermal absorption of C10-C12 is low with permeability coefficients inversely proportional to carbon number [3]. This conclusion is supported by a study showing that 95-98% of topically applied n-hexadecane did not penetrate fresh intact porcine skin regardless of vehicle utilized [4].

Absorption by inhalation for substances > C12, significant absorption by the inhalation route of exposure is expected to be limited on the basis of low vapor pressure.

Aliphatics in the C9 –C20 range (normal, iso) share a common metabolic profile. They are typically metabolized by side chain oxidation to alcohol and carboxylic acid derivatives. These metabolites can be glucuronidated and excreted in the urine or further metabolized before being excreted. The majority of the metabolites are excreted in the urine and to a lower extent, in the feces. Excretion is rapid with the majority of the elimination occurring within the first 24 hours of exposure. As a result of the lack of systemic toxicity and the ability of the parent material to undergo metabolism and rapid excretion, bioaccumulation of this carbon range in the tissues is not likely to occur [5; 6; 7; 8; 9; 10].

Conclusion on GS1927-GS2735 - toxicokinetics:

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively will have toxicokinetic properties similar to those alkene constituents already tested.

2.2 Acute toxicity

GTL gasoil and GTL kerosine indicate that GTL C9-C20 fractions are of low acute oral toxicity. They are not expected to be acutely toxic by the dermal or inhalation route because of their limited absorption through these routes and the limited vapor pressures. [11]

Oral LD50: > 5000 mg/kg bw [12; 13]

Dermal LD 50: > 2000 mg/kg bw [14]

Inhalation LD 50: LC50 (4 h): expected to be > 9300 mg/m³ (saturated vapour).

The vapour pressure of alkenes > C12 is low. Thus it is expected that based on oral and dermal acute data, acute inhalation toxicity will not be of concern. Hazards associated at high concentrations of a low volatile material will likely require generation of a mist resulting in aspiration hazard rather than acute toxicity. There is supporting evidence that inhalation of C10-C12 iso-alkanes at > 9300 mg/m³, which is a concentration near saturation did not result in toxicity relevant to humans [15]. Assessing inhalation toxicity at higher carbon chains and beyond ambient saturation is likely to cause aspiration artefacts' which are unrelated to direct acute toxicity.

GS 310 – Acute toxicity inhalation (aerosol)

GTL Solvent GS310 was tested for acute inhalation following a standard procedure (OECD 436, nose only). Because of its low vapour pressure (0.00031 Pa at 25°C), the material had to be tested as an aerosol [76], this form of exposure may happen in the workplace, but aerosol concentrations will be several orders of magnitude below the tested concentrations (see Appendix 1).

The material was tested in a group of six rats which were exposed to one of two aerosol atmosphere concentrations for 4 hours using a nose only exposure system. Exposure was followed by a 14 day observation period. Three deaths occurred in the group exposed to 4.98 mg/L, whereas, one death occurred at a 1.14 mg/l (3/6 and 1/6 deaths respectively).
Histopathology examinations however, reveal that the deaths are attributed to aspiration rather than systemic or acute toxicity. Therefore the acute inhalation median lethal concentration of 4.98 mg/l (4 hr LC50) which falls in the range of >1 - 5 mg/l, of acute inhalation toxicity category 4 – H332, should not merit classification. This is because the LC50 value obtained by exposure to an aerosol is not acute toxicity in itself but aspiration, which is induced by exposure conditions following study design and a function of low viscosity. This hazard is already recognised for low viscosity hydrocarbons and indicated as "Aspiration Hazard, category 1 – H304".

Conclusion on GS1927-GS2735 – acute toxicity:

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not acutely toxic by dermal, oral and vapor inhalation. In line with the results of GS310 and due to similar carbon number range, GS2735 may produce aspiration hazard when tested in aerosol form in an acute inhalation test, nose only.

2.3 Irritation and sensitization

2.3.1 Skin Irritation:

All GTL-Solvents were tested for skin irritation potential *in vivo* and *in vitro* following OECD 404 and 439 respectively [16 – 27]. Results on both data sets showed significant concordance, indicating that *in vitro* results are predictive for skin irritation potential. Positive results for irritation but not corrosion were observed for the C8-C11 *in vitro* and *in vivo* [17, 20]. Results of rabbit experiments indicate that the C9-C12 solvent is irritating [16], albeit with slightly lower erythema scores when compared to the scores

from the solvent C8-C11 (2.0 and 2.2 respectively as 24, 48 and 72 hrs. mean). These values alone are closer to the criteria for "mild irritant" – category 3 classification, but because skin effects were still noticed after the observation period, category 2 seemed more appropriate for classification. This could explain the negative results obtained on the C9-C12 solvent *in vitro* test; a careful look at the data indicates that although the relative mean tissue viability was decreased (59%), it was just above the 50% relative mean tissue viability threshold for irritancy classification [21]. It seems that *in vitro* tests can't distinguish between moderate and mild irritants. Thus taken all together the C9-C12 is irritating in animals, and slightly above the positive threshold *in vitro* indicating an inverse relationship between longer carbon chains (and higher boiling points) and irritating potential. Irritation is thus not observed in the C9-C13 solvent [22] or in longer carbon chains, indicating a clear break point for irritation potential at $\geq$ C13.

From the data on the tested solvents it can be concluded that the following solvents should be classified and labelled according to GHS as: Skin Irritation Category 2 - H315 *Causes skin irritation.*

- Hydrocarbons, C8-C11, n-alkanes, isoalkanes, <2% aromatics
- Hydrocarbons, C9-C12, n-alkanes, isoalkanes, <2% aromatics

Conclusion on GS1927-GS2735 – skin irritation:

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to be irritating to the skin because of the constituents' carbon chain length. The low end of the GS1927 (C11-C13) is covered by by an vivo test (C12-C15) and in vitro tests (C9-C13, C10-C13), which are negative [18 and 22,23], thus indicating that the low end of this solvent is not expected to contribute significantly to irritating the skin.

2.3.1 Eye Irritation:

All GTL-Solvents were tested for eye irritation potential in vivo and in vitro following OECD 405 and 437 respectively. Results on both data sets showed concordance, indicating that in vitro results are predictive for eye irritation potential. No corrosion or irritation was observed for any of the tested solvents, indicating that GTL solvents are not irritating to the eye [28-39]. No further testing is necessary.

Conclusion on GS1927-GS2735 – eye irritation:

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to be irritating to the eye.

2.3.3 Sensitisation:

Four GTL-Solvents with the carbon ranges C8-C11; C9-C12; C12-C15 and C18-C24 were tested in the Magnusson-Kligman Method following the OECD 406 guideline [40-43]. The selection of these solvents covers all carbon ranges by interpolation allowing robust read across. In these tests, animals were intradermally injected with a concentration of 20% or 50% in order to boost the animals' response to

the test material. Following being epidermally exposed at 20% to 100% concentration to induce sensitisation.

Two weeks after the epidermal application all animals were challenged with a 20% or 50% test substance concentration. In some cases (C9-C12 and C12-C15 fractions) a second challenge was performed one week later with the test substance concentration 20% and the vehicle in order to confirm that the observations of the first challenge were not due to sensitisation caused by the test material [41, 42].

All substances, including those tested at a second challenge were negative and thus not regarded as sensitising. The sensitisation rate in all cases was 0%.

Additional guinea pig data on a GTL product, with carbon rage C15-C27 which overlaps with the previously tested GTL-Solvents, is consistent with the conclusions that hydrocarbons of this types are not skin sensitisers [43].

Based on the available data set covering the low end (C8-C11 and C9-C12); middle chains (C12-C15); high end (C18-C24) and the overlapping C15-C27 carbon chain data, it is reasonable to interpolate these results to the following GTL-Solvents and waive additional guinea pig tests:

GTL Solvent GS190 (C10-C13); GTL Solvent GS210 (C9-C13); GTL Solvent GS250 (C14-C16); GTL Solvent GS270 (C15-C19) and GS1927, GS2735 with carbon ranges C11-C16 and C16-C22 respectively.

Conclusion on GS1927-GS2735 – skin sensitisation:

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to be sensitizing to the skin.

2.4 Repeated dose

Repeated exposure to aliphatic hydrocarbons in the C8-C24 range might result in any of the following systemic effects[2], which are considered non-adverse or irrelevant for human hazard assessment as explained below:

a.) increased liver weights (hepatocyte enlargement)

b.) kidney changes in male rats

c.) mesenteric lymph node granuloma or histiocytosis

[2] Other common effects related to manipulation or dosing techniques are not discussed here as they are not considered intrinsic toxicity effects of alkanes.

Justification:

a.) Increased liver weights are a common observation in repeated dose studies of aliphatic constituents. However, the histological investigations commonly report hepatocellular hypertrophy but not pathological changes; serum chemistry studies do not reveal increases in markers of liver damage; and reversibility of the liver weight and histological effects has been demonstrated in studies in which the animals were treated for 90 days and then held for 28 days without treatment [45]. These observations indicate that the increased liver weights are a compensatory effect and without toxicological consequence [46]. Further, alkane effects on liver enlargement appear to decrease with increasing carbon chain length based on a repeated dose study on GTL-Diesel, where the alkane peak is in the C18-C20 range. Liver weights (relative and absolute) were comparable to controls.

b.) Male rat kidney effects have been observed with some hydrocarbon solvents, particularly those with isoparaffinic and naphthenic constituents. These observations are part of a specific response of male rats to a group of structurally-similar substances (e.g. hydrocarbons) that induce an α2u-globulin-mediated nephropathy in male rats. These effects are observed in oral [47] as well as in inhalation studies [48] and are considered to be a gender- and species-specific process that is not relevant to humans [49; 50].

c.) Macrophage accumulation in the mesenteric lymph node appears to be a common finding in rat repeated toxicity studies with alkanes with carbon numbers of about C16 and above (not clear cut has been established) [50, 51]. Granulomas are discrete collections of macrophages occurring mostly in cortical and paracortical zones, in or adjacent to subcapsular or cortical sinuses. Another feature is the non-uniform distribution between the same or different nodes. When macrophages are mostly located in the medullary sinuses and are diffuse and loosely accumulated, the term histiocytosis is used. These findings also occur in controls and are not considered biologically adverse or relevant to humans [49]. Further, increases in histiocytes in mesenteric lymph nodes are considered a nominal effect to certain materials [50].

Conclusion on GS1927-GS2735 – repeated dose toxicity

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to have toxicological effects which are different to those observed in repeated dose toxicity studies on the basis of their alkane constituents following well understood metabolism, and systemic effects related to hydrocarbon exposure.

2.5 Mutagenicity and Carcinogenicity

2.5.1. Bacterial Tests

All GTL-Solvents were tested in the *Salmonella typhimurium* reverse mutation assay with four histidine-requiring strains of *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and in the *Escherichia coli* reverse mutation assay with a tryptophan-requiring strain of *Escherichia coli* (WP_2uvrA). The test

was performed in two independent experiments in the presence and absence of S9-mix (rat liver S9-mix induced by Aroclor 1254). The study procedures were based on the most recent OECD 471 guideline [52-59].

None of the tested GTL-Solvents induced a significant dose-related increase in the number of revertant (His+) colonies in each of the four tester strains (TA1535, TA1537, TA98 and TA100) and in the number of revertant (Trp+) colonies in tester strain WP2uvrA both in the absence and presence of S9-metabolic activation. These results were confirmed in an independently repeated experiment. All studies the negative and strain-specific positive control values were within the laboratory historical control data ranges indicating that the test conditions were adequate and that the metabolic activation system functioned properly.

It was concluded that all tested GTL-Solvents within the carbon range C8-C24 are not mutagenic in the Salmonella typhimurium reverse mutation assay and in the Escherichia coli reverse mutation assay.

2.5.2. Chromosome Aberration tests

GTL Solvents with carbon ranges C8-C11 and C9-C12 were tested *In vitro* in the Chromosome Aberration Test using human lymphocytes following OECD 473 [60-61].

In two independent experiments, neither a statistically significant nor a biologically relevant increase in the number of cells carrying structural chromosomal aberrations was observed after treatment with the test item. No evidence of an increase in polyploid metaphases was noticed after treatment with the test item as compared to the control cultures.

It was concluded that both GTL Solvents GS160 and GS170 did not induce structural chromosomal aberrations in human lymphocytes in vitro. Therefore, Hydrocarbons, C8-C12, are considered to be non-clastogenic in this chromosome aberration test.

Further experiments were carried out with the GTL solvents covering additional carbon ranges C13-C24. Some statistically significant increases were observed in some tests at a single test concentration, but since no dose response was observed, increases were not in the high dose and it was not due to S9 activation, it may be regarded as biologically irrelevant [65,67]. Thus by weight of evidence, the results from all fractions are indicative of a lack of clastogenicity in the chromosome aberration test [62-67]. In regards to The C18-C24 carbon range (GTL solvent GS-310) in the absence of S9 mix, one single increase in chromosomal aberrations, above the laboratory historical control data range, was observed after treatment at a dose below the highest tested concentration. The value is not statistically significant and no dose-dependency was observed. No evidence of an increase in polyploid metaphases was noticed after treatment with the test item as compared to the control cultures. In the presence of S9 mix no relevant increase in chromosomal aberrations was observed.

This increase response above controls at the same dose in two measurements has been taken into consideration for a confirmatory experiment. Such an increase has little biological meaning, as if there was a clastogenic effect one would expect a dose response pattern, statistically significance and positive

findings in the S9 fraction (which was negative at all concentrations). The experiment has been therefore interpreted as inconclusive and a confirmatory experiment is being undertaken [67].

2.5.3 Additional mutagenicity data

Additional supporting information from similar GTL products covering the carbon ranges C8-C26 is in alignment with the chromosome aberration test data generated for GTL Solvents C8-C11 and C9-C12. The *In vitro* data on GTL-gasoil and GTL-Kerosene in the micronucleus test [68, 69] and GTL-gasoil *in vivo* Bone Marrow Chromosome aberration Test [70] indicate that these aliphatic materials are not mutagenic.

From a read across perspective the data generated for GTL-Solvents are supported by results from similar GTL-products (e.g. Kerosene and Gas oil) with wider carbon ranges. Thus "read across" by interpolation to other solvents which fall within the carbon ranges of the tested materials is reasonable.

Further, there is no evidence from literature for alkanes (the only constituents of GTL-Solvents) indicating a carcinogenic potential, which is supported by the obtained negative mutagenicity data.

Conclusion on GS1927-GS2735 – mutagenicity and carcinogenicity

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to be mutagenic or carcinogenic based on their alkane constituents lacking structural alerts and negative results in GTL solvents and substances with a similar constituent's profile.

2.6 Reproductive and Developmental toxicity

In a two-generation reproductive toxicity study (OECD 416) with GTL Gasoil [71], there were no test item related effects on F1 and F2 litter parameters, postnatal survival, physical condition, mortality, pup body weights and anogenital distance. Equivocal, non-adverse decreases (not statistically significant) in absolute and relative spleen weights were observed in the F1 and F2 male and female PND 21 pups in the group given 750 mg/kg/day, compared with the control group. Macroscopic and microscopic findings in PND 21 pups were not test item related. NOAEL for developmental effects can therefore be considered to be at least 750 mg/kg bw/day (the highest dose tested).

C9-C13 alkanes was tested in a rat developmental toxicity (OECD 414) study via the inhalation route [72]. Pregnant rats were exposed at two nominal concentrations of 300 and 900 ppm for 6 hours per day during days 6 to 15 of gestation. At the high dose level there were signs of maternal respiratory irritation, indicating that a maximal inhalation concentration had been used. The NOAEL for developmental effects was greater than the highest concentration tested, 866 ppm (ca. 5 mg/l).

Conclusion on GS1927-GS2735 – reproductive toxicity

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected to be reproductive toxicants based on their composition and data on similar materials.

2.7 Acute CNS effects – Drowsiness and dizziness.

Acute CNS effects arising from hydrocarbon exposure are associated with generaluptake of hydrocarbons into the central nervous system. The toxicological effect is believed to be associated with changes in membrane fluidity and, for low molecular weight hydrocarbons, are associated with octanol/water partitioning. The hydrocarbons are distributed to and eliminated from the CNS relatively rapidly with elimination half-lives on the order of 2 hours. The hydrocarbons that cause acute CNS effects are the more volatile constituents, particularly those with carbon numbers from C6-C9 [73-75]

The hydrocarbon constituents with > 9 carbons have such low volatility that exposure by inhalation is limited, and, further, they do not easily pass the blood-brain barrier and achieving levels in the CNS sufficient to produce CNS effects is unlikely [11].

Conclusion on GS1927-GS2735 – acute CNS effects

GTL solvents GS1927 and GS2735 with carbon ranges C11-C16 and C16-C22 respectively are not expected cause acute CNS effects due to their carbon numbers >C9.

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[17] Latour 2014. PRIMARY SKIN IRRITATION/CORROSION STUDY WITH HYDROCARBONS, C8-C11, N-ALKANES, ISOALkanes, <2% AROMATICS IN THE RABBIT (SEMI-OCCLUSIVE APPLICATION). Wil Research Project 506342

[18] Latour 2014. PRIMARY SKIN IRRITATION/CORROSION STUDY WITH HYDROCARBONS, C12-C15, N-ALKANES, ISOALkanes, <2% AROMATICS IN THE RABBIT (SEMI-OCCLUSIVE APPLICATION). Wil Research Project 506343

[19] Latour 2014. PRIMARY SKIN IRRITATION/CORROSION STUDY WITH HYDROCARBONS, C18-C24, ISOALKANES, <2% AROMATICS IN THE RABBIT (SEMI-OCCLUSIVE APPLICATION). Wil Research Project 506344

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[21] Westerink 2014. IN VITRO SKIN IRRITATION TEST WITH HYDROCARBONS, C9-C12, N-ALKANES, ISOALKANES, <2% AROMATICS USING A HUMAN SKIN MODEL. Wil Research Project 506292

[22] Westerink 2014. IN VITRO SKIN IRRITATION TEST WITH HYDROCARBONS, C9-C13, N-ALKANES, ISOALKANES, <2% AROMATICS USING A HUMAN SKIN MODEL. Wil Research Project 506299

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Appendix 1

Hazard Classification of GTL solvent GS310 as "Acute Toxic by Inhalation" under GHS

Background:

Shell GTL Solvent GS310 is a low volatile hydrocarbon solvent (0.00031 Pa at 25°C).

For regulatory purposes, the substance was tested for acute inhalation following a standard procedure (OECD 436, nose only). Because of its low vapour pressure, the material had to be tested as an aerosol (Griffiths, 2014), this form of exposure may happen in the workplace, but aerosol concentrations will be several orders of magnitude below the tested concentrations.

The material was tested in a group of six rats which were exposed to one of two aerosol atmosphere concentrations for 4 hours using a nose only exposure system. Exposure was followed by a 14 day observation period.
The two aerosol atmosphere concentrations tested had mean concentrations of: 4.98 mg/l and 1.14 mg/l with respective mean mass aerodynamic diameter (µm) of 3.17 and 2.45.
Three deaths occurred in the group exposed to 4.98 mg/L, whereas, one death occurred at a 1.14 mg/l (3/6 and 1/6 deaths respectively) (see Appendix 1.1).

Following GHS classification and labelling rules, the acute inhalation median lethal concentration (4 hr LC50) of the tested solvent, is in the range of >1 - 5 mg/l.
Taken at face value, the data suggests that the obtained value of 4.98 mg/l falls in the GHS rage of "*category 4, acute toxicity*" for mists (1.0 < category 4 < 5.0 mg/l), and should therefore be classified as "Acute Inhalation toxicity; category 4 – H332".

A careful look at the histopathological examinations gives insight into the obtained results.
The microscopic findings observed in the lungs (alveolar and perivascular inflammation, edema, congestion and hemorrhage) were all consistent with inflammation (i.e. a chemical pneumonitis) induced by hydrocarbon aspiration.
Low viscosity hydrocarbon fluids, such as the tested GTL GS310 hydrocarbon solvent, are hazardous by aspiration (chemical pneoumonitis).
Thus, this may be the likely explanation for the observed toxicity; because of the high aerosol concentrations (5 mg/l) required to conduct these inhalation experiments, the aerosolized fluid may coalesce in the upper respiratory tract forming a film of fluid in the trachea, which leads to aspiration and the subsequent chemical pneumonitis. It should be noted that rats, unlike humans, are obligatory nasal breathers and have highly complex nasal turbinates compared to humans. These facts make that coalescence of aerosol droplets is much more likely to occur in rats upon inhalation of high concentrations of hydrocarbons than in humans. For these reasons, acute toxicity caused by inhalation of GTL products is considered to be a highly unrealistic scenario in humans (see Appendix 1.3).

The low acute toxicity of this type of hydrocarbons is supported by comparison to other routes of exposure and study design. Assuming worst case scenario, if this material was tested with the highest achievable vapour concentration, the maximum total inhaled dose would be ~ 0.01 mg/kg body weight, which is orders of magnitude lower than acute oral toxicity dose with GTL Diesel (feedstock for GTL GS310) where bioavailability is the greatest and no toxicity was observed at doses as high as 5,000 mg/kg (see Appendix 1.2).

Conclusion:

Because of the low vapour pressure and thus very low internal dose that can be achieved by vapour exposure; the material was tested by means of generating an aerosol. Albeit technically possible and in line with the OECD guideline 436, it doesn't reflect real life exposure conditions.
Following GHS classification and labelling rules, the acute inhalation median lethal concentration (4 hr LC50) of the tested solvent, is in the range of >1 - 5 mg/l, which would merit classification as acute inhalation toxicity category 4 – H332.
Histopathology examinations however, reveal that the deaths are attributed to aspiration rather than systemic or acute toxicity.
Therefore, the LC50 value obtained by exposure to an aerosol is not acute toxicity in itself but aspiration, which is induced by exposure conditions following study design. This hazard is already recognised for low viscosity hydrocarbons and indicated as "Aspiration Hazard, category 1 – H304", which my occur by accidental ingestion but not at regular occupational exposures that are orders of magnitude lower than the LC50 value ~ 5000 mg/m^3
Saturated air concentration of GS310 *vapours* are calculated at 0.04 mg/m^3; the highest *aerosol* levels are expected during spraying operations and are conservatively estimated at 1.1 mg/m^3 .

Based on the evidence, the intrinsic hazard of GS310 is already accounted for by classifying "Aspiration Hazard, category 1 – H304", and having an additional "acute inhalation hazard category 4", is not only redundant but also confusing for hazard communication.
In conclusion, the exposure by inhalation of GS310 under different formulations and settings, including aerosol, should be of no concern.

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Appendix 1.1
Study results

Shell GTL Solvent GS310 was tested in one acute inhalation toxicity (nose only) study in the rat following OECD 436.

A group of six rats (three males and three females) were exposed to one of two aerosol atmosphere concentrations (one group per concentration). The two aerosol atmosphere concentrations tested had mean concentrations of: 4.98 mg/l and 1.14 mg/l with respective mean mass aerodynamic diameter (µm) of 3.17 and 2.45.

The animals were exposed for four hours using a nose only exposure system, followed by a fourteen day observation period.

Three deaths occurred in the group exposed to 4.98 mg/L, whereas, one death occurred at a 1.14 mg/l (3/6 and 1/6 deaths respectively).

Dark patches on the lungs were noted at necropsy amongst all three surviving animals at 4.98 mg/l and in one out of five surviving animals at 1.14 mg/l. A further surviving female at 4.98 mg/l exhibited a dark liver at the end of the fourteen day recovery period.

Dark patches in the lungs and abnormally dark lungs in both treatment groups were associated with congestion at histopathological examination, and were considered to be treatment-related.

Due to the observations noted it was considered that the deaths noted during the study may have been mainly attributable to local toxicity.

The microscopic findings observed in the lungs (alveolar and perivascular inflammation, edema, congestion and hemorrhage) were all consistent with hydrocarbon aspiration induced inflammation (i.e. a chemical pneumonitis), rather than being indicative of systemic or acute toxicity.

It was therefore considered that the acute inhalation median lethal concentration (4 hr LC50) of Shell GTL Solvent GS310, in the rat, was in the range of >1 - 5 mg/l.

These results are in line with what was observed with GTL Diesel, the feedstock for GS310.
GTL diesel was first tested at 5.61 mg/l, which was higher than the target concentration of 5.0 mg/l. At this concentration, one out of three male rats and one out of three female rats died. The surviving animals showed transient adverse effects but recovered completely within 8 to 9 days. The study was then repeated at a slightly lower concentration of 5.11 mg/l; none of the male rats and only one out of three female rats died and the surviving animals recovered fully with 7 to 8 days. Gross pathology did not show any systemic toxicity but the lungs were dark coloured or had dark patches. Detailed histopathology showed pulmonary congestion and oedema with clear signs of inflammation consistent with aspiration toxicity. The LC50 value was estimated at > 5 mg/L (4 h).

In conclusion, in all acute inhalation studies with GTL products where toxicity was observed, the histopathology showed that there were only effects in the lung, compatible with hydrocarbon aspiration induced chemical pneumonitis. The absence of other systemic effects is highly indicative that mortality is due to aspiration, due to coalescence of the aerosol droplets forming a film of the fluid in the upper respiratory tract, rather direct toxicity. It should be noted that rats, unlike humans, are obligatory nasal breathers and have highly complex nasal turbinates compared to humans. These facts make that coalescence of aerosol droplets is much more likely to occur in rats upon hydrocarbon aerosol inhalation than in humans, favoured by study design. For these reasons, and the expected real life exposures, acute toxicity caused by inhalation of GTL products is considered to be a highly unrealistic scenario in humans

Appendix 1.2

Internal dose by maximum achievable vapour concentrations

For the rationale, GTL GS310 hypothetical internal dose is calculated
The vapour pressure of this GTL GS310 is 0.00031 Pa at 25 ºC.

This vapour pressure can be converted into a concentration using the relationship between vapour pressure and concentration defined for any gas by the equation:

$$p = nRT/V$$

where p is the pressure in Pa, V is the volume in cubic metres, T is the temperature in degrees Kelvin (degrees Celsius + 273.15), n is the quantity of gas expressed in molar mass (g / Mw), R is the gas constant: 8.31 Joules/mol/m^3

To convert the vapour pressure to concentration in g/m^3 the following formula is used:

$$(g / Mw) / V = p / RT$$

At 25˚C (298 K), R*T = 2,478 JKm^3/mol, the equation rearranged to (Mw*p)/RT = g/V
Then it follows that the air concentration equals (Mw * 0.00031) / 2,478 = g/m3.

On that basis the following gas quantity is used based on the molecular weight of GS310:

Mw = 255 – 339 g/mol
(300 g/mol is taken as average)

Hence, based on an average Mw of 300 g/mol for GS310, and its established vapour pressure of 0.00031 Pa at 25˚C, the saturated concentration in the vapour phase is: (300 * 0.00031) / 2,478 = 0.04 mg/m^3

Considering that a rat with a body weight of 250 g inhales approximately 12 litres of air ($0.012m^3$) per hour, in a standard acute inhalation study according to the OECD 403 guidelines (4 h of exposure) the approximately inhaled amount of GTL GS310 would be (0.012 m^3/h * 0.04 mg/m^3 * 4 h) = **0.002 mg**. Based on an average body weight for a rat of 250 g, the maximum total inhaled dose would be **~ 0.01 mg/kg** body weight.

It should be born in mind that this calculation is assuming worst-case exposure conditions at the maximum vapour pressure including full retention and 100% absorption in the lungs.
Bearing in mind that in acute oral toxicity studies with GTL Diesel (feedstock for GS310) where bioavailability is the greatest, no toxicity was observed at doses of 5,000 mg/kg (Sanders A., 2006), it follows that inhalation exposures are several orders of magnitude below a dose which did not show any systemic or local toxicity. Thus vapours of GTL GS310 should not be considered acute toxicants.

Because of the low vapour pressure and thus very low internal dose that can be achieved by vapour exposure; the material was tested by means of generating an aerosol. Albeit technically possible and in line with the OECD guideline 436, it is unrealistic in real life exposure conditions and applications.

Appendix 1.3
Exposure estimates

As has been explained in Appendix 1.2, GS310 has a low vapour pressure (0.00031 Pa at 25˚C). The expected saturated air concentration is 0.04 mg/m^3, which should not be of concern for applications where only vapour exposure is expected.

For applications where an aerosol can be formed, and in view of the 4 hr LC50, which is in the range of >1 - 5 mg/l (>1000 – 5000 mg/m^3) exposure modelling is necessary to assess the potential risk of being exposed to concentrations which would be in the range of the LC50 value.
Additionally, aerosol concentrations should be below the Occupational Exposure Level (OEL). There is no actual OEL value for GS310, but based on composition and viscosity, the mineral oil OEL = 5 mg/m^3 was used as a surrogate.

The following parameters were used:

Material: GTL GS310

Model: Advanced REACH Tool

Exposure settings: worker exposure during applications expected to give the highest exposure levels.

- Pesticide spraying
- metal working fluid mists.

The assumption is that GS310 will be used in formulations between 90-100%. This is conservative, but illustrative to assume worse case scenarios.

Exposure p oint values are 75-percentile estimates, numbers in brackets is the interquartile confidence interval.

Pesticide spraying (up to 90% GS310):

a. Pesticide backpack spraying, 8 hours, outdoors, no control in place: **0.44 mg/m3** (0.19-1.0)
b. Pesticide open tractor (no cabin) spraying (fogging), outdoors, no controls in place: **0.38 mg/m3** (0.17-0.86)
c. Pesticide spraying in tractor cabin (fogging) outdoors, no control: **0.27 mg/m3** (0.12-0.61)

Metal working fluids (up to 100% GS310):

d. Use in large scale applications indoor normal mechanical ventilation and enclosure during operation: **0.5 mg/m3** (0.24 – 1.1 mg/m^3)

Using the highest value of the interquartile confidence interval, uncontrolled spraying pesticide applications with GS310 at 90% could be about 1.0 mg/m^3 . This level is below the OEL of 5 mg/m^3 and 3 orders of magnitude below the LC50 1000 – 5000 mg/m^3 . This is also true for the highest calculated value in metal working applications (1.1. mg/m^3).

In conclusion, estimated vapour and aerosol exposures of GS310 remain below the OEL and 3 orders of magnitude below the LC50, indicating that exposure to GS310 by inhalation should be of no concern.